

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number  
WO 2004/007498 A3

(51) International Patent Classification<sup>7</sup>: C07D 487/04,  
519/00, A61K 31/53, A61P 35/00

(21) International Application Number:  
PCT/EP2003/050292

(22) International Filing Date: 8 July 2003 (08.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
02077823.9 15 July 2002 (15.07.2002) EP

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

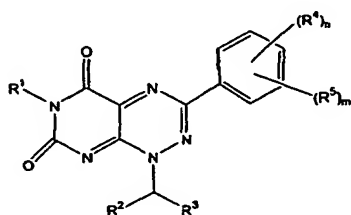
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

# Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,

[Continued on next page]

(54) Title: 3-PHENYL ANALOGS OF TOXOFLAVINE AS KINASE INHIBITORS



(1)

(57) Abstract: The present invention concerns the compounds of formula (I) the N-oxide forms, the pharmaceutically acceptable addition salts and the stereo-chemically isomeric forms thereof, wherein n represents an integer being 0, 1 or 2; m represents an integer being 0 or 1; R<sup>1</sup> represents C<sub>1-4</sub>alkyl; R<sup>2</sup> represents C<sub>1-4</sub>alkyl; R<sup>3</sup> represents C<sub>1-4</sub>alkyl; or R<sup>2</sup> and R<sup>3</sup> taken together with the carbon atom to which they are attached form a C<sub>3-8</sub>cycloalkyl or Het<sup>1</sup> wherein said C<sub>3-8</sub>cycloalkyl or Het<sup>1</sup> each independently may optionally be substituted with C<sub>1-4</sub>alkyloxycarbonyl; R<sup>4</sup> represents halo or C<sub>1-4</sub>alkyloxy; R<sup>5</sup> represents C<sub>1-4</sub>alkyloxycarbonyl, -O-(mono- or di(C<sub>1-4</sub>alkyl)aminosulfonyl),

C<sub>1-4</sub>alkyl substituted with one or where possible more substituent being selected from Het<sup>3</sup> or NR<sup>6</sup>R<sup>7</sup>, C<sub>1-4</sub>alkyloxy substituted with one or where possible more substituents being selected from amino, Het<sup>4</sup> or NR<sup>8</sup>R<sup>9</sup>; R<sup>6</sup> and R<sup>7</sup> are each independently selected from hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl, -Het<sup>5</sup> or C<sub>1-4</sub>alkyl substituted with one or where possible more substituents being selected from hydroxy, or Het<sup>5</sup>; R<sup>8</sup> and R<sup>9</sup> are each independently selected from hydrogen, C<sub>1-4</sub>alkyl, -Het<sup>7</sup> or mono- or di(C<sub>1-4</sub>alkyl)aminosulfonyl; Het<sup>3</sup> represents a heterocycle selected from piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, aminosulfonyl, amino, mono- or di(C<sub>1-4</sub>alkyl)aminosulfonyl, hydroxyC<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkyloxy; Het<sup>4</sup> represents a heterocycle selected from morpholinyl, piperidinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxycarbonyl or mono- or di(C<sub>1-4</sub>alkyl)aminosulfonyl; Het<sup>5</sup> represents a heterocycle selected from pyridinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl, or mono- or di(C<sub>1-4</sub>alkyl)aminosulfonyl; Het<sup>7</sup> represents piperidinyl.



KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
8 July 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50292

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 C07D519/00 A61K31/53 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Derwent Publications Ltd., London, GB; AN 1998-011934 XP002261586 -&amp; JP 09 255681 A (TAISHO PHARM CO) cited in the application abstract page 4-6</p> <p style="text-align: center;">--- -/--</p>	1-12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

26 April 2004

Date of mailing of the international search report

14 05 2004

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50292

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAGAMATSU, TOMOHISA; YAMASAKI, HIROFUMI: "FACILE AND GENERAL SYNTHESSES OF 1-ALKYLTOTOXOFLAVIN AND 8-ALKYLFERVENULIN DERIVATIVES OF BIOLOGICAL SIGNIFICANCE BY THE REGIOSPECIFIC ALKYLATION OF REUMYCIN (1-DEMETHYLTOTOXOFLAVIN, 8-DEMETHYLFERVENULIN) DERIVATIVES" HETEROCYCLES, vol. 45, no. 4, 1997, pages 643-650, XP001154789 page 650, paragraph 14	1-12
X	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 05, 30 June 1995 (1995-06-30) - & JP 07 041479 A (TAISHO PHARMACEUT CO LTD), 10 February 1995 (1995-02-10) abstract page 5-8	1-12
X	NAGAMATSU, TOMOHISA; YAMASAKI, HIROFUMI: "General syntheses of 1-alkyltoxoflavin and 8-alkylfervenulin derivatives of biological significance by the regioselective alkylation of reumycin derivatives and the rates of transalkylation from 1-alkyltoxoflavins into nucleophiles" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, vol. 2, 2001, pages 130-137, XP002261583 cited in the application page 130-131	1-12
X	NAGAMATSU T ET AL: "SYNTHESSES OF 3-SUBSTITUTED 1-METHYL-6-PHENYLPYRIMIDINE-5,4-E-1,2,4- TRIAZINE-5,7(1H,6H)-DIONES (6-PHENYL ANALOGS OF TOXOFLAVIN) AND THEIR 4-OXIDES, AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF TOXOFLAVINS AND THEIR ANALOGS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 41, no. 2, 1993, pages 362-368, XP001036979 ISSN: 0009-2363 cited in the application page 362-364	1-12

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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1977:43663            XP002261584            abstract; example 148            &amp; YONEDA ET AL.: JOURNAL OF THE CHEMICAL            SOCIETY, CHEMICAL COMMUNICATIONS,            vol. 16, 1976, pages 658-659,</p>	1-12
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1974:120872            XP002261585            abstract; example 190            &amp; YONEDA ET AL.: JOURNAL OF HETEROCYCLIC            CHEMISTRY,            vol. 11, no. 1, 1974, pages 83-85,</p>	1-12
X	<p>WO 02/20525 A (LIM KAH LEONG ;YEO SU LING            (SG); TAN YIN HWEE (SG); WANG HAISHAN ())            14 March 2002 (2002-03-14)            claim 1</p>	1-12
A	<p>US 6 174 889 B1 (COCKERILL GEORGE STUART            ET AL) 16 January 2001 (2001-01-16)            column 1-2; claim 1</p>	1-12
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1977:139991            XP002277970            abstract; examples 141-145            &amp; YONEDA ET AL.: JOURNAL OF THE CHEMICAL            SOCIETY, PERKIN TRANSACTIONS 1,            vol. 22, 1976, pages 2398-2402,</p>	1-12
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1976:421301            XP002277971            abstract; examples 155-159            &amp; YONEDA ET AL.: JOURNAL OF THE CHEMICAL            SOCIETY, PERKIN TRANS. 1,            vol. 7, 1976, pages 713-715,</p>	1-12

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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1992:633685            XP002277972            abstract; examples 135,136            &amp; SMIRNOVA ET AL.: KHIMIYA            GETEROTSIKLICHESKIKH SOEDINENII,            vol. 2, 1992, pages 219-224,</p>	1-12
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1976:17293            XP002277973            abstract; examples 160-162            &amp; YONEDA ET AL.: BULL. CHEM. SOC.,            vol. 48, no. 10, 1975, pages 2884-2887,</p>	1-12
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1976:4913            XP002277974            abstract; examples 163-177            &amp; YONEDA ET AL.: CHEM. PHARM. BULL.,            vol. 23, no. 9, 1975, pages 2001-2009,</p>	1-12
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1975:443279            XP002277975            abstract; examples 179-183            &amp; YONEDA ET AL.: SYNTHESIS,            vol. 3, 1975, pages 177-179,</p>	1-12
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1974:491479            XP002277976            abstract; examples 184-189            &amp; YONEDA ET AL.: J. HET. CHEM.,            vol. 11, no. 2, 1974, pages 271-273,</p>	1-12
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1973:466325            XP002277977            abstract; examples 197-200            &amp; YONEDA ET AL.: TET. LETT.,            vol. 17, 1973, pages 1577-1580,</p>	1-12
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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50292

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>           DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            Database accession no. 1971:405866            XP002277978            abstract; examples 201-204            &amp; YONEDA ET AL.: TET. LETT.,            vol. 13, 1971, pages 851-854,  <u>          </u> </p>	1-12

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/50292

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claim : 1(part)

Compounds according to claim 1 in which m and n are 0 (the group of compounds is not unitary but was searched without extra effort).

2. Claim : 1(part)

Compounds according to claim 1 comprising at least one substituent R4 or R5 (the group of compounds is not unitary but can be searched without extra effort).

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/50292

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 09255681	A	30-09-1997	NONE	
JP 07041479	A	10-02-1995	NONE	
WO 0220525	A	14-03-2002	AU 9353801 A WO 0220525 A2 CA 2421718 A1	22-03-2002 14-03-2002 14-03-2002
US 6174889	B1	16-01-2001	AT 249458 T AU 3443997 A BR 9710359 A DE 69724789 D1 EP 0912570 A1 JP 2000514445 T NO 990124 A CA 2260061 A1 CN 1230187 A CZ 9900089 A3 WO 9802438 A1 EP 1304110 A2 HR 970371 A1 ID 19403 A KR 2000023812 A PL 331221 A1 TR 9900049 T2 US 6723726 B1 ZA 9706146 A	15-09-2003 09-02-1998 17-08-1999 16-10-2003 06-05-1999 31-10-2000 11-03-1999 22-01-1998 29-09-1999 16-06-1999 22-01-1998 23-04-2003 31-08-1998 09-07-1998 25-04-2000 05-07-1999 21-04-1999 20-04-2004 11-01-1999